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Induction of chronic relapsing experimental allergic encephalomyelitis in Biozzi mice.

Baker D, O'Neill JK, Gschmeissner SE, Wilcox CE, Butter C, Turk JL.

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Department of Pathology, Royal College of Surgeons of England, London, U.K.

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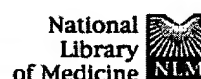
Experimental allergic encephalomyelitis (EAE) was induced in Biozzi AB/H (antibody high) mice by sensitization with spinal cord homogenate in adjuvant. Biozzi AB/H mice were highly susceptible to EAE induction and followed a chronic relapsing pattern of disease. Disease episodes were characterized by mononuclear infiltration of the central nervous system, with demyelination being particularly evident in relapse. The cellular infiltrates, which were associated with immunoglobulin deposition, consisted of macrophages and primarily CD4-positive T lymphocytes. However, similarly treated Biozzi AB/L (antibody low) mice were markedly less susceptible to EAE induction than AB/H mice. Thus, Biozzi mice should prove valuable for the study of chronic relapsing EAE.

PMID: 2373763 [PubMed - indexed for MEDLINE]

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Prevention of experimental autoimmune encephalomyelitis in the common marmoset (*Callithrix jacchus*) using a chimeric antagonist monoclonal antibody against human CD40 is associated with altered B cell responses.

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Boon L, Brok HP, Bauer J, Ortiz-Buijsse A, Schellekens MM, Ramdien-Murli S, Blezer E, van Meurs M, Ceuppens J, de Boer M, 't Hart BA, Laman JD.

Tanox Pharma B.V., Amsterdam, The Netherlands.

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Inhibition of CD40-CD40 ligand interaction is a potentially effective approach for treatment of autoimmune diseases, such as multiple sclerosis. We have investigated this concept with a chimeric antagonist anti-human CD40 mAb (ch5D12) in the marmoset monkey experimental autoimmune encephalomyelitis (EAE) model. Marmosets were immunized with recombinant human myelin oligodendrocyte glycoprotein (rMOG) and treated from the day before immunization (day -1) until day 50 with either ch5D12 (5 mg/kg every 2-4 days) or placebo. On day 41 after the induction of EAE, four of four placebo-treated monkeys had developed severe clinical EAE, whereas all animals from the ch5D12-treated group were completely free of disease symptoms. High serum levels of ch5D12 associated with complete coating of CD40 on circulating B cells were found. At necropsy placebo- and ch5D12-treated animals showed similar MOG-specific lymphoproliferative responses in vitro, but ch5D12 treatment resulted in strongly reduced anti-MOG IgM Ab responses and delayed anti-MOG IgG responses. Most importantly, treatment with ch5D12 prevented intramolecular spreading of epitope recognition. Postmortem magnetic resonance imaging and immunohistologic analysis of the CNS showed a markedly reduced lesion load after ch5D12 treatment. In conclusion, the strong reduction of clinical, pathological, and radiological aspects of EAE by ch5D12 treatment in this preclinical model points to a therapeutic potential of this engineered antagonist anti-CD40 mAb for multiple sclerosis.

PMID: 11509643 [PubMed - indexed for MEDLINE]

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S6	32	RD S5 (unique items)
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11285610 EMBASE No: 2001295316

Prevention of experimental autoimmune encephalomyelitis in the common marmoset (*Callithrix jacchus*) using a chimeric **antagonist** monoclonal antibody against human **CD40** is associated with altered B cell responses

Boon L.; Brok H.P.M.; Bauer J.; Ortiz-Buijsse A.; Schellekens M.M.; Ramdien-Murli S.; Blezer E.; Van Meurs M.; Ceuppens J.; De Boer M.; 'T Hart B.A.; Laman J.D.

Dr. J.D. Laman, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam Netherlands

AUTHOR EMAIL: laman@immu.fgg.cucr.nl

Journal of Immunology (J. IMMUNOL.) (United States) 01 SEP 2001, 167/5 (2942-2949)

CODEN: JOIMA ISSN: 0022-1767

DOCUMENT TYPE: Journal ; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 32

Inhibition of CD40-CD40 ligand interaction is a potentially effective approach for treatment of autoimmune diseases, such as multiple sclerosis. We have investigated this concept with a chimeric **antagonist** anti-human **CD40** mAb (ch5D12) in the marmoset monkey experimental autoimmune encephalomyelitis (EAE) model. Marmosets were immunized with recombinant human myelin oligodendrocyte glycoprotein (rMOG) and treated from the day before immunization (day - 1) until day 50 with either ch5D12 (5 mg/kg every 2-4 days) or placebo. On day 41 after the induction of EAE, four of four placebo-treated monkeys had developed severe clinical EAE, whereas all animals from the ch5D12-treated group were completely free of disease symptoms. High serum levels of ch5D12 associated with complete coating of CD40 on circulating B cells were found. At necropsy placebo- and ch5D12-treated animals showed similar MOG-specific lymphoproliferative responses in vitro, but ch5D12 treatment resulted in strongly reduced anti-MOG IgM Ab responses and delayed anti-MOG IgG responses. Most importantly, treatment with ch5D12 prevented intramolecular spreading of epitope recognition. Postmortem magnetic resonance imaging and immunohistologic analysis of the CNS showed a markedly reduced lesion load after ch5D12 treatment. In conclusion, the strong reduction of clinical, pathological, and radiological aspects of EAE by ch5D12 treatment in this preclinical model points to a therapeutic potential of this engineered **antagonist anti-CD40 mAb for multiple sclerosis.**

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12330308 BIOSIS NO.: 200000083810

IL-12 reverses the **suppressive** effect of the **CD40** ligand
blockade on experimental autoimmune encephalomyelitis (EAE).

AUTHOR: Constantinescu Cris S; Hilliard Brendan; Wysocka Maria; Ventura
Elvira S; Bhopale Mahendra K; Trinchieri Giorgio; Rostami A M(a)

AUTHOR ADDRESS: (a)Department of Neurology, University of Pennsylvania,
Philadelphia, PA, 19104**USA

JOURNAL: Journal of the Neurological Sciences 171 (1):p60-64 Dec. 1, 1999

ISSN: 0022-510X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Blockade of the **CD40** ligand (CD40L)-**CD40** interaction
suppresses experimental autoimmune encephalomyelitis (EAE). Since
this interaction induces IL-12, an essential cytokine for EAE induction,
we hypothesized that CD40L blockade may suppress EAE through IL-12
inhibition. Here we show that exogenous IL-12 abolishes the ability of
anti-CD40L monoclonal antibodies to prevent EAE. Anti-IL-12 antibodies
prevent this reversal and protect from EAE. These results show that IL-12
is sufficient to overcome CD40L blockade and suggest that, of the
multiple consequences of the CD40L-CD40 interaction, IL-12 induction is
an essential one for induction of EAE.

/3 (Item 3 from file: 5)
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13071609 BIOSIS NO.: 200100278758

The critical role of TNF-alpha in IFN-gamma-induced CD40 expression in macrophages and microglia.

AUTHOR: Nguyen Vince T(a); Benveniste Etty N(a)

AUTHOR ADDRESS: (a)University of Alabama at Birmingham, 1918 University Blvd, MCLM338, Birmingham, AL, 35294**USA

JOURNAL: FASEB Journal 15 (4):pA708 March 7, 2001

MEDIUM: print

CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001

ISSN: 0892-6638

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: CD40 is a type I membrane bound molecule belonging to the Tumor Necrosis Factor Receptor (TNFR) superfamily. Cells expressing CD40 include B cells, dendritic cells, macrophages, microglia and a variety of tumor cells. CD40 expression on professional antigen presenting cells (APCs) such as dendritic cells, macrophages and B cells has been demonstrated to be crucial for T cell activation. Aberrant expression of CD40 has been associated with autoimmune inflammatory diseases such as **multiple sclerosis** and rheumatoid arthritis. We have recently shown that the cytokine IFN-gamma is the most potent inducer of CD40 expression in macrophages and microglia. This induction is mediated by the IFN-gamma-activated transcription factor STAT-1alpha and the constitutively expressed transcription factors PU.1 and/or Spi-B. In this study, we have discovered that a major component of IFN-gamma induced **CD40** expression involves the production of the cytokine TNF-alpha. The inclusion of anti-TNF-alpha antibody **inhibits** apprx65% of IFN-gamma induced **CD40** gene expression. TNF-alpha activation of the transcription factor NF-kappaB is important for optimal **CD40** expression. Inclusion of dominant negative constructs against IKK-alpha or IKK-beta **inhibits** IFN-gamma-induced **CD40** promoter activity. Furthermore, we have identified NF-kappaB elements in the **CD40** promoter that are functionally important for IFN-gamma-induced CD40 expression. These results indicate that a paracrine response to TNF-alpha is an integral part of the mechanism of IFN-gamma-induced CD40 expression in macrophages/microglia.